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Predictors of Late Cardiovascular Complications in Survivors of Hematopoietic Cell Transplantation

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Long-term survival after hematopoietic cell transplantation (HCT) is now an expected outcome. The growing population of survivors is at risk of developing treatment-related complications, including cardiovascular disease (CVD). A nested case-controlled design was used to identify clinical and treatment-related risk factors for development of late (1+ years after HCT) CVD. Cases were identified from a cohort of 1+-year survivors who underwent transplantation at City of Hope between 1977 and 2006. Controls (HCT survivors without CVD) were matched on age, year of HCT, type of HCT, and duration of follow-up. Sixty-three patients with late CVD were identified, 44 (69.8%) with a coronary artery event and 19 (30.2%) with a cerebrovascular event. Median age at HCT was 49.0 years. Median age at onset of late CVD was 54.0 years; 66.7% of the affected patients had undergone autologous HCT. Multivariate logistic regression analysis showed that the presence of multiple cardiovascular risk factors (2 or more of the following: obesity, dyslipidemia, hypertension, and diabetes) after HCT was associated with a 5.2-fold increased risk of late CVD ($P < .01$), and that pre-HCT chest radiation exposure was associated with a 9.5-fold greater risk of coronary artery disease ($P = .03$). Pre-HCT exposure to chest radiation and the presence of comorbidities were primarily responsible for the risk associated with late CVD after HCT. These data form the basis for developing predictive models for identifying high-risk individuals for targeted surveillance and aggressive management of comorbidities.

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INTRODUCTION

Hematopoietic cell transplantation (HCT) is the treatment of choice for many hematologic malignancies. Advances in HCT strategies have contributed to an incremental improvement in survival of 10% per decade [1]. This improvement is not enjoyed equally by all individuals, however. A growing population of long-term survivors is at risk for developing treatment-related complications [2-4].

One of the more serious complications is therapy-related cardiovascular disease (CVD) [5,6]. Previous reports indicate that cardiovascular events, including cerebrovascular disease (eg, stroke, transient ischemic attack [TIA], carotid arterial occlusion, symptomatic lacunar infarcts), and coronary artery disease (eg, myocardial infarction, atherosclerotic heart disease, angina pectoris) are prevalent and often occur earlier than expected in the general population [3,7,8]. The cumulative incidence of CVD approaches 23% at 25 years after HCT in certain high-risk populations, and the incidence appears to increase with time [8]. The risk of CVD is reportedly greatest in recipients of allogeneic HCT [3]. Such factors such as increasing age, hypertension, diabetes, dyslipidemia, high body mass index (BMI), and male sex are known to modify the risk of CVD in the general population [9,10]. HCT survivors are known to be at an increased risk for developing diabetes and hypertension, which potentially can contribute to the risk of CVD in this population [3]. Finally, HCT recipients are at a 2.3- to 4.0-fold increased risk of death because of cardiac causes compared with the general population [11,12]. Taken together, these reports provide evidence for the fact that CVD is a significant contributor to post-HCT morbidity and mortality, and that the risk of CVD potentially could be modified by the presence of comorbidities.

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To date, few studies have conducted a comprehensive evaluation of the risk factors associated with the development of CVD after HCT, and none has evaluated the role of pre-HCT therapeutic exposure. The reports describing this outcome are hampered by small sample size [3,7,8,13], and the contribution of comorbidities to the risk of CVD among HCT survivors has not yet been fully explored. In the current study, we addressed these gaps by evaluating the role of pre- and post-HCT therapeutic exposures (ie, chemotherapy and radiation), transplantation-related conditioning, and post-HCT comorbidities in the development of CVD in a large cohort of long-term HCT survivors.

METHODS

This study used a nested case-controlled design. The sampling frame for the cases and controls comprised a retrospectively constructed cohort of 3287 consecutive patients who had undergone HCT for a hematologic malignancy at City of Hope (COH) between 1977 and 2006 and had survived for at least 1 year. A long-term follow-up (LTFU) form was completed for each of the 3287 patients in this cohort. Information collected on the LTFU form included demographic data, disease status, medication, hospitalization, and post-HCT complications, including CVD, and details regarding graft-versus-host disease (GVHD). This information was merged with data from an institutional database on HCT-related exposures, such as conditioning and GVHD prophylaxis/treatment. The LTFU form captured information regarding post-HCT complications beginning at 1 year posttransplantation through the date of last contact.

Medical records maintained at COH were the primary source of data for completing the LTFU forms. If a patient's last medical visit was not recent, or if there were any unexpected gaps in a patient's history within the follow-up period of interest, then a standard protocol was used to identify and contact any physicians treating the patient outside COH to obtain pertinent information. If the physician was not available or was unable to provide recent information, then the patient was called directly. This method of follow-up ensured that information regarding CVD was captured in an uninterrupted fashion from 1 year post-HCT to the date of last contact with a health care provider. The COH Human Subjects Committee approved the study protocol. Informed consent was provided in accordance with the Declaration of Helsinki.

To be eligible for consideration as a case, a patient had to have developed CVD (coronary artery or cerebrovascular disease) 1 or more years after HCT. Controls (between 1 and 3) were selected at random from the same cohort and matched to cases for age at HCT ($\pm$ 5 years), year of HCT ($\pm$ 2 years), donor source (autologous vs allogeneic), and duration of follow-up (control follow-up exceeded matched case follow-up).

Exposure Variables

For both cases and controls, medical records from COH and other institutions (if indicated) were used to abstract clinical and therapeutic information during the pre-HCT, conditioning, and post-HCT periods. The following data were collected: demographic information, disease characteristics, pre-HCT therapeutic exposures (chemotherapy: cumulative dose per square meter body surface area; radiation therapy: total dose, field, and dose per fraction), conditioning regimen (chemotherapeutic agents; total body irradiation [TBI]: number of fractions and total dose).

Therapeutic exposures were summarized for cases and controls. An anthracycline cardiotoxicity risk score [14] was calculated by multiplying the cumulative dose of each anthracycline (ie, doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone) by a factor reflecting the cardiotoxic potential of each drug and then summing the individual scores. A cumulative alkylating agent dose was calculated by multiplying the cumulative dose of each alkylating agent (ie, cyclophosphamide[Cy], procarbazine, ifosfamide, dacarbazine, busulfan, carmustine, lomustine, and melphalan) by a factor reflecting its acute hematotoxic potential and again summing the individual scores [15,16] (see Supplement, Table 1). Chest radiation included mantle (standard and modified), mediastinal, and lung radiation; neck radiation broadly included cervical, parotid, nasopharynx, and extended mantle radiation.

Cardiovascular Risk Factors

Comorbidities developing before or after HCT were identified through medical record abstraction. A patient's comorbidities were captured if diagnosed by the treating physician and/or if the patient was tasking medications for their management. To be considered a post-HCT event, a comorbidity had to be diagnosed after the HCT, but before the onset of CVD. Furthermore, the comorbidity had to be active at the time of the event (cases) or for a comparable period of follow-up (controls).

Separate pre-HCT and post-HCT cardiovascular risk scores were calculated by assigning a point for each of the following comorbidities, all of which are well-recognized risk factors for CVD: hypertension, dyslipidemia, diabetes, and obesity (BMI >30 kg/m^2 at HCT) [7,10]. Patients with a cardiovascular risk score ≥ 2 were considered at high risk for CVD [7,10,17].

Table 1. Characteristics of the Patient Population and Pre-HCT Exposure

Characteristic	Cases (n = 63)*	Controls (n = 186)*	P Value
Age at initial diagnosis, years, mean (SD)	47.8 (13.0)	47.3 (12.5)	.69
Male sex, n (%)	43 (68.3)	96 (51.6)	.03
Ethnicity/race, n (%)			
Non-Hispanic white	47 (74.6)	119 (64.0)	.14
Others	16 (25.3)	67 (36.0)	
Diagnosis, n (%)†			
Lymphoma	27 (42.9)	67 (36.0)	.31
Non-Hodgkin lymphoma	23 (36.5)	57 (30.6)	
Hodgkin lymphoma	4 (6.3)	10 (5.4)	
Nonlymphoma	36 (57.1)	119 (64.0)	
Multiple myeloma	12 (19.0)	43 (23.1)	
Acute lymphoblastic leukemia	4 (6.3)	11 (5.9)	
Acute myelogenous leukemia	10 (15.9)	33 (17.7)	
Chronic myelogenous leukemia	9 (14.3)	16 (8.6)	
Other	1 (1.6)	16 (8.6)	
Pre-HCT comorbidity, No. (%)			
Smoking, ever	31 (49.2)	75 (40.3)	.27
Hypertension	16 (25.4)	24 (12.9)	.03
Dyslipidemia	6 (9.5)	12 (6.5)	.41
Diabetes	3 (4.8)	9 (4.8)	.99
Pre-HCT therapy			
Anthracycline, mg/m2, mean (SD)	205.1 (140.9)	177.8 (139.4)	.18
Alkylating agent, g/m2, mean (SD)	4.2 (7.8)	3.2 (9.6)	.43
Cisplatin, mg/m2, mean (SD)	60.0 (139.5)	48.4 (121.1)	.38
Cranial radiation, n (%)	2 (3.2)	7 (3.8)	.84
Neck radiation, n (%)	2 (3.2)	6 (3.2)	.99
Chest radiation, n (%)	5 (7.9)	6 (3.2)	.17

SD indicates standard deviation; HCT, hematopoietic cell transplantation.
*Group matching criteria included age at HCT (±5 years), type of HCT (autologous vs allogeneic), year of HCT (± 2 years), and duration of follow-up.
†Analyzed as lymphoma (non-Hodgkin lymphoma, Hodgkin lymphoma) versus nonlymphoma (multiple myeloma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, and other).

Outcome Variable: Late Cardiovascular Event

Late CVD events were defined as cardiovascular events developing 1+ years after HCT and were classified as coronary artery disease (ie, myocardial infarction, angina pectoris, or symptomatic atherosclerotic heart disease [coronary artery narrowing >50%]) or cerebrovascular disease (ie, stroke, TIA, symptomatic lacunar infarct, or symptomatic carotid artery occlusion [>50% narrowing] necessitating surgical intervention) in accordance with the American College of Cardiology's (ACC) established case definitions and clinical data standards for coronary artery and cerebrovascular disease [18-20]. Cerebrovascular events were excluded if they resulted from thrombocytopenia or clotting factor deficiency or were from central nervous system (CNS) trauma, infection, or active CNS disease.

Statistical Analysis

Cases and controls were compared in terms of demographics, pre-HCT therapeutic exposures, HCT-related conditioning, and pre- and post-HCT cardiovascular risk factors, using conditional logistic regression for categorical variables and linear regression adjusting for matching sets for continuous variables. For the purpose of this analysis, primary diagnoses were categorized into 2 groups: lymphoma (ie, non-Hodgkin lymphoma [NHL] and Hodgkin lymphoma [HL]) and nonlymphoma (ie, multiple myeloma, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, and other diagnoses).

Multivariate conditional logistic regression was used to identify variables that were significantly and independently associated with CVD after HCT. Variables included were those significantly associated with CVD on univariate analysis, as well as those considered to have an impact on the clinical outcome but that were not part of the matching criteria. The regression model included sex, ethnicity (non-Hispanic white vs other), smoking history (never vs ever), diagnosis (lymphoma vs nonlymphoma), pre- and post-HCT cardiovascular risk factors (dichotomized as <2 vs ≥2 conditions), conditioning with chemotherapeutic agents (no vs yes), TBI (no vs yes), and age at diagnosis (continuous variable). Separate regression models also were created for coronary artery and cerebrovascular disease to identify risk factors that might be unique to these outcomes. For the coronary artery disease model, pre-HCT chest radiation exposure was added to the model; for the cerebrovascular disease model, pre-HCT head and neck radiation exposure were added. An alpha level of <.05 was considered significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Sixty-three cases with late CVD and 186 matched controls were included in the analysis. Sixty-one cases (97%) had 3 matched controls. The median follow-up after HCT was 7.3 years (range, 1.3-29.8 years) for cases and 8.2 years (range, 1.4-30.4 years) for controls; 37% of cases and controls were 10+-year survivors.

Patient Characteristics

Table 1 summarizes the clinical characteristics of cases and controls. Cases were significantly more likely to be male (68.3% vs 51.6%; $P = .03$). There were no significant differences between cases and controls with respect to age at diagnosis, race/ethnicity, or underlying diagnoses. Among allogeneic HCT recipients, there were no differences between cases and controls with respect to the prevalence of acute GVHD or of previous or active chronic GVHD (data not shown).

Therapeutic Exposures

The interval between the diagnosis of primary disease and HCT was comparable in the cases and

controls (1.8 years vs 1.5 years; $P = .24$) (Table 2). There were no significant differences between cases and controls with respect to cumulative exposure to anthracycline, alkylating agents, or cisplatin, or to exposure to cranial, neck, or chest radiation. When data were analyzed separately for coronary artery and cerebrovascular events, pre-HCT exposure to chest radiation was more prevalent in cases with coronary artery disease compared with controls (11.4% vs 2.3%; $P = .01$); median chest radiation dose was equivalent in the 2 groups (40 Gy [range, 24-42 Gy] vs 40 Gy [range, 36-40 Gy]). There were no significant differences in the proportion of patients treated with cranial (8.8% vs 5.3%; $P = .62$) or neck (5.3% vs 3.5%; $P = .73$) radiation between cases with cerebrovascular disease and matched controls.

Cy (63.1%), etoposide (53.0%), and TBI (53.0%) were the most commonly used conditioning agents. Cases were significantly more likely than controls to have received Cy as part of their conditioning regimen (71.4% vs 60.2%; $P = .04$) (Table 2). There were no significant differences between the 2 groups with respect to all other conditioning exposures.

Table 2. HCT Conditioning Regimens and Post-HCT Outcomes

Characteristic	Cases (n = 63)*	Controls (n = 186)*	P Value
Age at HCT, years, mean (SD)	49.6 (13.0)	48.8 (12.3)	
Autologous donor source, n (%)	42 (66.7)	123 (66.1)	
Time from diagnosis to HCT, years, mean (SD)	1.8 (3.6)	1.5 (1.7)	.24
Body mass index at HCT, kg/m^2, mean (SD)	28.5 (6.4)	26.6 (5.0)	.01
Conditioning regimen			
Cyclophosphamide	45 (71.4)	112 (60.2)	.04
Etoposide	33 (52.4)	99 (53.2)	.79
TBI	34 (54.0)	98 (52.7)	.78
Melphalan	15 (23.8)	60 (32.3)	.09
Carmustine	10 (15.9)	22 (11.8)	.46
Busulfan	8 (12.7)	24 (12.9)	.99
Post-HCT comorbidities			
Hypertension	23 (36.5)	35 (18.8)	<.01
Dyslipidemia	21 (33.3)	28 (15.1)	<.01
Diabetes	13 (20.6)	20 (10.8)	.05
Cardiovascular risk†			
<2 conditions	50 (84.1)	169 (91.9)	<.01
≥2 conditions	10 (15.9)	15 (8.1)	

SD indicates standard deviation; HCT, hematopoietic cell transplantation; TBI, total body irradiation.

*Group matching criteria included: age at HCT (±5 years), type of HCT (autologous vs allogeneic), year of HCT (±2 years), and duration of follow-up.

†Conditions included hypertension, dyslipidemia, diabetes, and obesity (BMI >30 kg/m^2) at HCT

Cardiovascular Risk Factors

Pre-HCT Cardiovascular Risk Factors

Cases were significantly more likely than controls to have been diagnosed with hypertension before HCT (25.4% vs 12.9%; $P = .03$) and to have a higher BMI at the time of HCT (28.5 kg/m^2 vs 26.6 kg/m^2; $P = .01$). There were no significant differences between the 2 groups in the prevalence of other cardiovascular risk factors before HCT.

Post-HCT Cardiovascular Risk Factors

With equivalent follow-up, cases were significantly more likely than controls to have hypertension (36.5% vs 18.8%; $P < .01$), dyslipidemia (33.3 vs 15.1; $P < .01$), and diabetes (20.6 vs 10.8; $P = .05$) (Table 2). Cases also were significantly more likely than controls to have multiple post-HCT cardiovascular risk factors (15.9 vs 8.1; $P < .01$). There were no differences between the 2 groups with respect to prevalence of immunosuppressive therapy at the time of cardiovascular risk assessment for allogeneic HCT recipients (52.4% vs 44.4%; $P = .53$).

Clinical Presentation of Late CVD

Of the 63 cases with late CVD, 44 (69.8%) presented with clinically documented coronary artery disease (myocardial infarction, n = 32; atherosclerotic heart disease, n = 9; angina pectoris, n = 3), and 19 (30.2%) presented with cerebrovascular disease (TIA, n = 9; stroke, n = 7; symptomatic carotid artery stenosis, n = 3). All met the clinical diagnostic criteria in accordance with the ACC's established case definitions and clinical data standards for coronary artery and cerebrovascular disease [18-20]. The median time to CVD was 4.0 years after HCT (range, 1.15-19.4 years), and the median age at presentation was 54.0 years (range, 25.0-82.4 years). None of these cases exhibited clinical evidence of CVD during the first year after HCT.

Of the 63 patients with late CVD, 34 have died. Overall survival following diagnosis of CVD (cases) and comparable follow-up (controls) was significantly worse for cases compared with controls (52.4% vs 80.6% at 5 years; $P < .01$). For cases, the most common causes of mortality were relapse/progression of primary disease (34.6%), cardiovascular events (30.7%), and infection (15.0%). For controls, relapse/progression of primary disease (69.8%) and infection (12.4%) were the most common causes of death.

Risk Factors for Late CVD

As shown in Table 3, multivariate conditional logistic regression revealed that the presence of 2 or more of the 4 targeted cardiovascular risk factors (ie, obesity, dyslipidemia, hypertension, and diabetes) was significantly and independently associated with a >5-fold (odds ratio [OR], 5.2; $P < .01$) increased risk of CVD. Furthermore, conditioning with Cy trended toward an increased risk for late CVD (OR, 2.5; $P = .06$).

Table 3. Multivariate Analysis of Risk Factors Associated with Late CVD

Risk Factor	OR	95% CI	*P* Value
Sex			
Female	1.0		
Male	1.6	0.80-3.21	.18
Ethnicity			
Others	1.0		
Non-Hispanic white	1.8	0.87-3.68	.12
Age at diagnosis		0.96-1.17	.23
Smoking			
Never	1.0		
Ever	1.3	0.67-2.38	.46
Diagnosis*			
Nonlymphoma	1.0		
Lymphoma	0.8	0.31-1.97	.60
Pre-HCT cardiovascular risk factors			
<2 conditions	1.0		
≥2 conditions	0.8	0.25-2.65	.74
Conditioning chemotherapy			
No cyclophosphamide	1.0		
Cyclophosphamide	2.5	0.94-6.66	.06
TBI			
No TBI	1.0		
TBI	1.0	0.47-2.24	.94
Post-HCT cardiovascular risk factors			
<2 conditions	1.0		
≥2 conditions	5.2	2.14-12.83	<.01

HCT indicates hematopoietic cell transplantation; TBI, total body irradiation.

*Analyzed as lymphoma (non-Hodgkin lymphoma, Hodgkin lymphoma) versus nonlymphoma (multiple myeloma, acute lymphoblastic leukemia, acute myelogeous leukemia, chronic myelogenous leukemia, and other).

Coronary Artery Disease

Multivariate analysis restricted to cases with coronary artery disease and their matched controls revealed that pre-HCT exposure to chest radiation (OR, 9.5; $P = .03$) and the presence of multiple post-HCT cardiovascular risk factors (OR, 4.8; $P < .01$) were associated with increased risk.

Cerebrovascular Disease

The presence of multiple post-HCT cardiovascular risk factors was associated with a 19.5-fold risk of late cerebrovascular disease (OR, 19.5; $P = .02$). Exposure to neck radiation (OR, 0.9; $P = .97$) and cranial radiation (OR, 0.1; $P = .20$) were not associated with increased risk.

DISCUSSION

The overall goal of this study was to conduct comprehensive evaluation of the impact of therapeutic exposures (pre-HCT, HCT-related conditioning, and post-HCT) and cardiovascular risk factors on the risk of late CVD in long-term survivors of HCT. To date, few studies have evaluated late-onset coronary artery events or stroke, in part because of the length and thoroughness of follow-up necessary to document these outcomes. Our study is the first to incorporate pre-HCT therapeutic exposures, conditioning, and post-HCT exposures and comorbidities to create a comprehensive risk profile for late CVD. We found that, other than a 9.5-fold increased risk of coronary artery disease with pre-HCT exposure to chest radiation, the risk of late-onset CVD is related primarily to cardiovascular risk factors developing after HCT.

It is increasingly recognized that atherosclerosis is an inflammatory process, with endothelial injury occurring several years before clinically evident CVD develops [21-23]. Whereas endothelial injury can occur acutely after treatment with high-dose alkylator- or platinum-based chemotherapy, long-term follow-up of non-HCT populations, such as HL [24], breast cancer [25], and testicular cancer [26] survivors, has shown that the risk of late-onset CVD is due primarily to chest radiation exposure, not to systemic chemotherapy. Radiation-induced vascular injury is characterized by endothelial cell proliferation, intimal thickening, medial scarring, lipid deposits, and adventitial fibrosis [27]; this process forms the basis for the ensuing atherogenesis and plaque formation in these long-term survivors [27]. In non-HCT populations, the risk of mortality from myocardial infarction after chest radiation exposure ranges from 2.2- to 7.2-fold over that of age- and sex-matched controls [28]; individuals at highest risk are those treated at age >21 years, with higher doses of radiation (>40 Gy), and those treated during an earlier era (<1985) [24,27,28]. In the current study, we found a 9.5-fold increased risk of coronary artery disease in survivors treated with chest radiation, after adjustment for demographics, treatment era, other therapeutic (pre-HCT chemotherapy, conditioning) exposures, and cardiovascular risk factors. Unlike previous reports [29,30], we were unable to demonstrate an association between cerebrovascular disease and cranial or neck radiation.

Well-established cardiovascular risk factors, such as insulin resistance with compensatory hyperinsulinemia, impaired glucose tolerance, hypertriglyceridemia, hypertension, and central obesity, are being increasingly reported after HCT [3,31-34]. Dyslipidemia, glucose intolerance, and hypertension can be consequences of prolonged immunosuppressive therapy after allogeneic HCT, exposure to TBI, or other conditions, such as growth hormone deficiency or hypothyroidism [6]. In conventionally treated cancer populations, cardiovascular risk factors are known to modify the risk of CVD [24-26]. The study of Dorresteijn et al. [35] was one of the first to report an increased risk of CVD in long-term cancer survivors, demonstrating a 12-fold increased risk of stroke in head and neck cancer survivors with diabetes or hypertension compared with survivors without these risk factors, and the magnitude of risk increased with increasing duration of follow-up. Later studies in HL

survivors [24,30,36] and breast cancer survivors [25] confirmed that certain chronic health conditions, such as hypertension, diabetes, and dyslipidemia, significantly increase the risk of CVD, even after adjustment for well-recognized demographic (age, sex), lifestyle (smoking history), and therapeutic (ionizing radiation) risk factors. These findings have formed the basis for current recommendations for screening and cardiovascular risk reduction in childhood and adult-onset cancer survivors [28,37,38].

Few studies have explored this association in HCT survivors, however. A recent report found a greater risk of CVD in allogeneic HCT recipients and in those with multiple cardiovascular risk factors [8]. In another study limited to allogeneic HCT recipients, older age at HCT and having multiple cardiovascular risk factors were the only significant predicators of self-reported late cardiovascular events [7]. In the current study, HCT survivors with CVD were significantly more likely to have multiple cardiovascular risk factors, resulting in a >5-fold increased risk of CVD. In fact, having a high cardiovascular risk score was associated with a 20-fold increased risk of cerebrovascular complications, such as stroke or TIA, after HCT.

High-dose Cy is commonly used as part of conditioning regimens for HCT. Cardiotoxicity associated with high-dose Cy is typically acute and dose-dependent, and ranges from asymptomatic electrocardiographic changes to pancarditis and congestive heart failure [6,39]. Whether subclinical myocardial injury sustained during conditioning contributes to the acceleration of atherosclerotic disease after HCT is unclear. Preliminary studies suggest that patients treated with high-dose Cy have higher numbers of circulating endothelial cells immediately after conditioning [40,41]. These endothelial cells may reflect disruption of the microvascular bed, leading to accelerated thrombus formation [40,41]. The role of Cy-induced endothelial injury in initiating clinically significant CVD years after HCT is not well defined. In the current study, conditioning with cyclophosphamide was associated with a 2.5-fold higher risk of CVD, an association that approached statistical significance.

Any retrospective review of medical records is limited by the amount of information available for review. As such, we were not able to reliably ascertain information regarding other cardiovascular risk factors, such as currency of smoking or pack-years of tobacco exposure, as well as details regarding physical activity. However, the prevalence of *any* smoking was equivalent to previous reports from similar populations [24,30] and was included in the final multivariate analysis model. Other studies using self-reported information from a similar population have demonstrated that the large majority of HCT survivors quit smoking after HCT, with <15% reporting current tobacco use [7,42]. The cases included in this study had clinically overt coronary artery or cerebrovascular disease. No individuals who may have had asymptomatic CVD were included. The focus of this study was on developing a deeper understanding of the impact of HCT-related exposures and comorbidities on the development of clinically overt cardiovascular events, and asymptomatic CVD does not fit this definition.

In summary, our findings indicate that pre-HCT exposure to chest radiation and the development of multiple cardiovascular risk factors post-HCT are primarily responsible for the high risk of CVD in HCT survivors. Although it appears that conditioning with high-dose Cy might have contributed to an increased risk, more studies are needed to evaluate the role of conditioning exposures in initiating clinically significant CVD in the post-HCT setting. These data form the basis for developing predictive models for identifying high-risk individuals to conduct targeted surveillance, as well as to develop preventive strategies in the form of aggressive management of comorbidities.

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